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DYKAT of Baylis−Hillman Adducts: Concise Total Synthesis of Furaquinocin E

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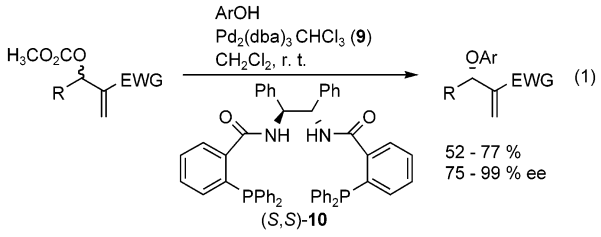
The furaquinocins (**1**−**8**; Figure 1) are a class of antibiotics isolated from the fermentation broth of *Streptomyces* sp. KO-3998 by Omura et al.[1] They show a wide range of biological effects, including in vitro cytotoxicity against HeLa S3 and B16 melamona cells, antihypertensive activity, and inhibition of platelet aggregation and coagulation. All members of the furaquinocins share a densely functionalized naphthoquinone core, differing only in the degree of oxidation of the isoprenoid side chain. The biological activity, as well as the challenging structural features, make this class of compounds highly interesting synthetic targets. Smith et al. reported a short chiral-pool-based synthesis of furaquinocin C (**3**),[2] and Suzuki et al. prepared the furaquinocins A (**1**), B (**2**), D (**4**), and H (**8**).[3] In this communication, we describe a conceptually new approach to this class of compounds that has great flexibility in generating various furaquinocins as well as analogues. It is based on a dynamic asymmetric kinetic transformation (DYKAT) process[4] and exemplified in the total synthesis of furaquinocin E (**5**).

The lack of adequate methods for an asymmetric Baylis−Hillman reaction precludes its use for asymmetric synthesis.[5] Our recent development of an efficient procedure for deracemization of Baylis−Hillman adducts as shown in eq 1[6] provides an opportunity to change this circumstance. The furaquinocins become an excellent target for such a protocol where these compounds can be accessed from the building blocks I, II, and III (Figure 2) based upon the Moore−Liebeskind naphthoquinone synthesis and the Pd-catalyzed asymmetric allylic alkylation (AAA).

The synthesis started with the dialkylation of 2-iodoresorcinol (**12**) with the allylic carbonate **11** (Scheme 1). The desired product **13** was obtained in excellent yield and good stereoselectivity (dr 92/8). The yield of the reaction is remarkable. In contrast to our previously reported examples, no formation of the regioisomer resulting from the attack of the phenol at the terminal position was observed. The following reductive Heck reaction proceeded with poor reproducibility when standard conditions ($PdCl_2(CH_3CN)_2$, HCOOH, TEA, DMF, 50 °C) were used.[8] Competing pathways



are the 6-*endo*-cyclization and the reionization of the substrate. Switching to the sterically hindered base pentamethylpiperidine (PMP) led to great improvement in yield and reproducibility. After

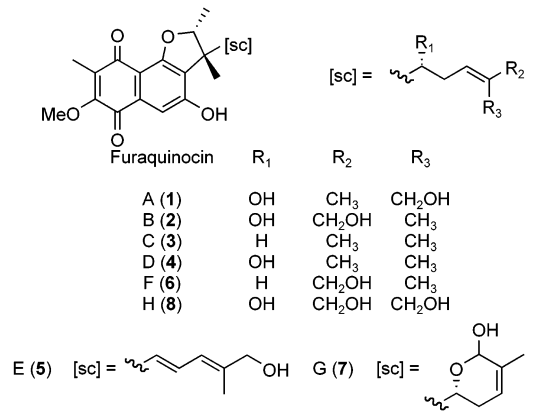


Figure 1. The furaquinocins.

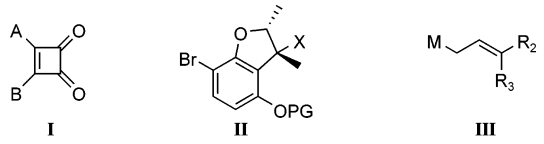
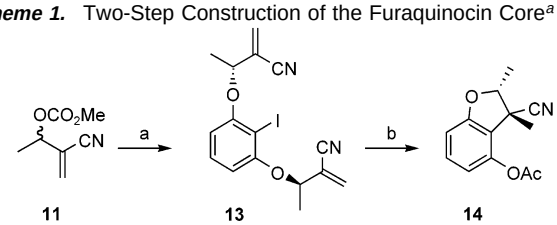


Figure 2. Synthons for furaquinocin synthesis.

Scheme 1. Two-Step Construction of the Furaquinocin Core[a]



[a] Conditions: (a) **12**, $Pd_2(dba)_3{\cdot}CHCl_3$ (1 mol %), ligand (*R*,*R*)-**10** (2.65 mol %), CH_2Cl_2, room temperature, 97%, dr 92/8. (b) (i) $PdCl_2(CH_3CN)_2$ (10 mol %), HCOOH, PMP, DMF, 50 C; (ii) Ac_2O, TEA, DMAP, CH_2Cl_2, room temperature, 81%, 87% ee (99% ee after recrystallization).

acetylization of the free phenol, the desired diasteromer **14** was obtained in very good yield. The relative stereochemistry was established by nOe-experiments and finally confirmed by single-crystal X-ray structure analysis (see the Supporting Information). The enantiomeric excess established in the allylic alkylation was determined to be 87%. Recrystallization of the acetate **14** led to enantiopure material.

Having established the two stereogenic centers in a very efficient manner, the stage was set for functionalization of the aromatic ring and the introduction of the unsaturated side chain (Scheme 2). Saponification of the acetate, TIPS-protection of the free phenol, followed by regioselective bromination with NBS led to compound **17**. Reduction of the nitrile to the corresponding aldehyde followed by Wittig−Horner−Emmons reaction with phosphonate **18**[9] yielded the desired (*E*,*E*)-diene **19** exclusively. Reduction of the methyl

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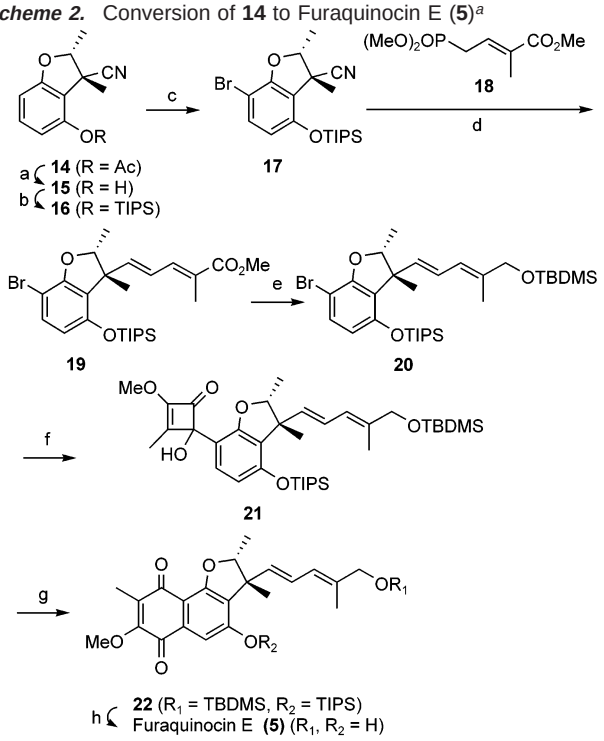
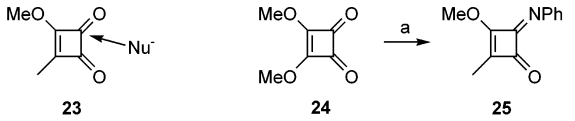
Scheme 2. Conversion of **14** to Furaquinocin E (**5**)[a]



[a] Conditions: (a) NaOMe, MeOH, room temperature, 94%. (b) TIPSOTf, TEA, CH_2Cl_2, 96%. (c) NBS, THF, room temperature, 92%. (d) (i) DIBAL, CH_2Cl_2, − 78 °C; (ii) **18**, LHMDS, THF, 0 °C, 89% (two steps). (e) (i) DIBAL, CH_2Cl_2, − 78 °C; (ii) TBDMSCl, imidazole, CH_2Cl_2, reflux, 89% (two steps). (f) (i) *n*-BuLi, THF, − 78 °C; (ii) **25**, THF, −78 °C; (iii) oxalic acid, THF/H_2O, 50%. (g) (i) toluene, 110 °C; (ii) air, room temperature, 64%. (h) TBAF, THF, 0 °C, 65%.

Scheme 3. Squaric Acid Derivatives[a]



[a] Conditions: (a) (i) MeLi, THF, −100 °C; (ii) TFAA, −78 °C; (iii) aniline, −78 °C to −15 °C (53%).

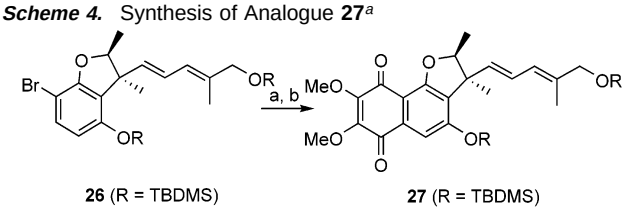
ester to the alcohol, followed by TBDMS-protection, afforded the advanced intermediate **20**.

Squaric acid-based methodology is available for the construction of naphthoquinones.[7] Use of the simple derivative **23** leads to nucleophilic attack of a organometallic compound on the ketone adjacent to the methoxy group (Scheme 3). After rearrangement and oxidation, this would furnish a naphthoquinone which would be regioisomeric to the furaquinocins concerning the substituents on the quinone. To reverse the regioselectivity, a temporary protection group was introduced.[10] Imine **25** could be obtained in good yield, through a one-pot procedure.

Halogen−metal exchange on bromine **20** and addition of the generated organolithium to imine **25**, followed by hydrolysis of the imine under mild acidic conditions, led to the addition product **21** in acceptable yield. All efforts to improve the yield, by using cerium- or magnesium-derived organometallics, failed. Thermal rearrangement followed by oxidation in air delivers the desired regioisomer of naphthoquinone **22**. After deprotection of the silyl ethers, furaquinocin E (**5**) is obtained. The spectroscopic data are in full agreement with those published for the natural product.[1d]

To illustrate the flexibility of our strategy, an analogue was prepared (Scheme 4). The intermediate **26** in the enantiomeric series was obtained by the route described herein and by using the (*S*,*S*)-

Scheme 4. Synthesis of Analogue **27**[a]



[a] Conditions: (a) (i) *n*-BuLi, THF, −78 °C; (ii) **24**, THF, −78 °C, 79%. (b) (i) PhCl, reflux; (ii) air, room temperature, 53%.

ligand **10**. Using dimethylsquarate **24** for the construction of the naphthoquinone gave **27**.

The asymmetric palladium-catalyzed alkylation of phenols combined with a reductive Heck reaction delivers an efficient approach to the core structure of the furaquinocins. The use of a protected squaric acid derivative allows the regioselective construction of the naphthoquinone. These reactions were highlighted in a short asymmetric synthesis of furaquinocin E. The flexibility of our approach should also allow for the synthesis of the other furaquinocins, by changing the side-chain fragment, as well as of analogues involving the quinone moiety. Efforts along this way are currently pursued.

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Supporting Information Available: Characterization data for **5**, **11**, **13**−**17**, **19**−**20**, **22**, **25**−**27** (PDF) and X-ray structure of **14** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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